



Mechanisms of Antimicrobial Resistance

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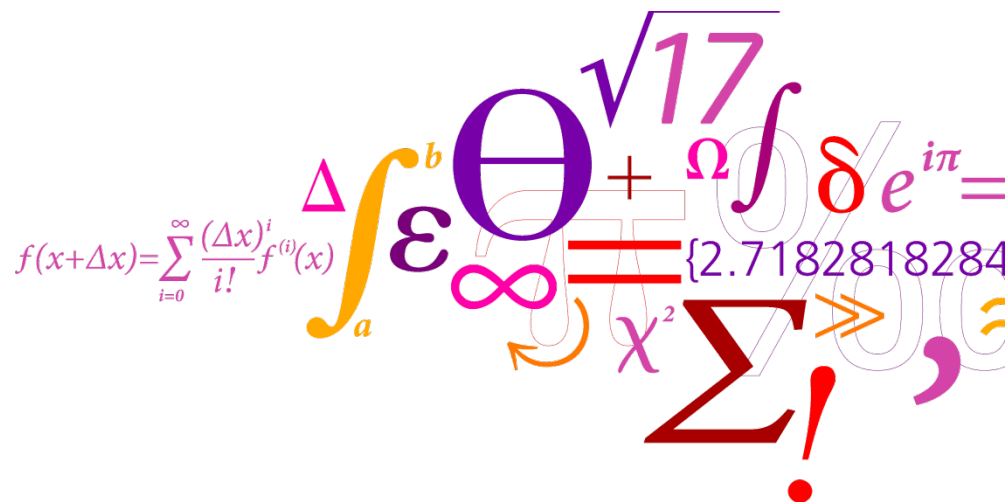
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Mechanisms of antimicrobial resistance

March, 2011 – Kolkata, India

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An antibiotic

...is a substance produced by a microorganism, that has the capacity, in dilute solution, to selectively inhibit or kill other microorganisms (Paul Vuillemin 1941)

An 'antimicrobial agent'

...refers to any substance that can affect microbial life - including synthetic and semi-synthetic substances and compounds without selective toxicity (e.g. disinfectants)

Origin and activity

Class	Origin	Activity
Aminoglycosides	<i>Streptomyces</i> sp, <i>Micromonospora</i> sp	Bactericidal
Cephalosporins	<i>Cephalosporium</i> spp	Bactericidal
Macrolides	<i>Streptomyces</i> spp	Bacteriostatic
Penicillins	<i>Penicillium</i> sp	Bactericidal
Phenicol	<i>Streptomyces venezuelae</i>	Bacteriostatic
Quinolones	Synthetic	Bactericidal
Rifamycins	<i>Amiclatopsis mediterranei</i>	Bactericidal
Sulfonamides	Synthetic	Bacteriostatic
Tetracyclines	<i>Streptomyces</i> spp	Bacteriostatic

What is antimicrobial resistance?

Microbiological definition:

- Resistance is the property of a bacterial strain to survive at higher antibiotic concentrations compared to most other members of the same species (wild types)

Clinical definition:

- Resistance is the ability of a bacterial strain to survive antimicrobial therapy

Intrinsic resistance

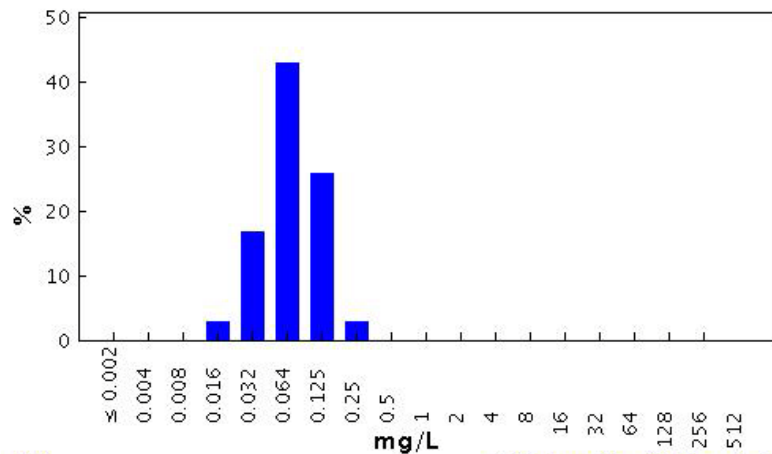
Resistance due to a structural or functional trait allowing tolerance by all members of a bacterial group (species, genus or even larger group)

- Impermeability
- Active exporters
- Enzymatic degradation
- Low affinity of the target

Example of intrinsic resistance

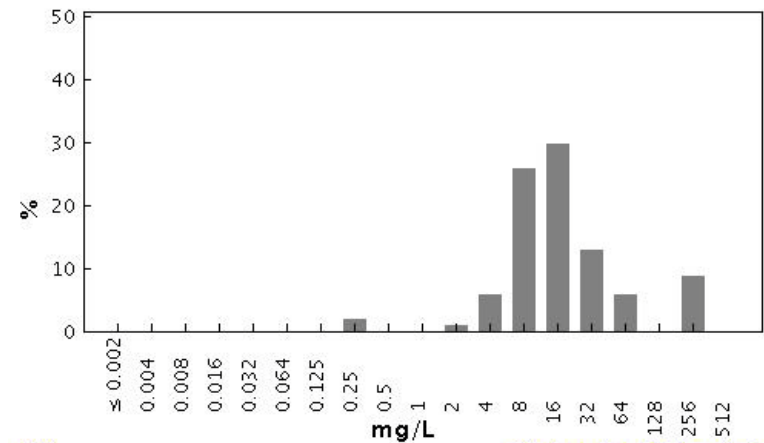
Cefotaxime susceptibility in *E. coli* and *Acinetobacter baumannii*

Cefotaxime / *Escherichia coli*
Antimicrobial wild type distributions of microorganisms – reference database
EUCAST



MIC
Epidemiological cut-off: WT ≤ 0.25 mg/L
3781 observations (11 data sources)
Clinical breakpoints: S ≤ - mg/L, R > - mg/L

Cefotaxime / *Acinetobacter baumannii*
Antimicrobial wild type distributions of microorganisms – reference database
EUCAST



MIC
Epidemiological cut-off: -
861 observations (2 data sources)
Clinical breakpoints: S ≤ - mg/L, R > - mg/L

Types of acquired resistance

Mutation (endogenous, vertical)

Gene transfer (exogenous, horizontal)

- Transformation (free DNA)
- Transduction (with phages)
- Conjugation (plasmids)

U.S. Department of Health & Human Services

FDA U.S. Food and Drug Administration

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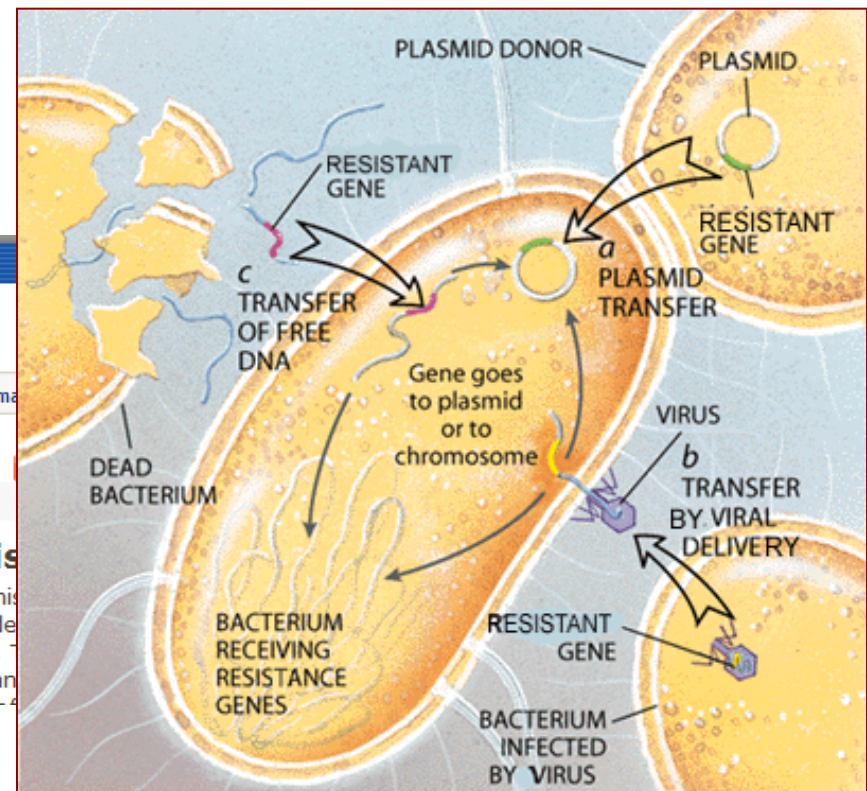
Safety & Health

▶ **Antimicrobial Resistance**

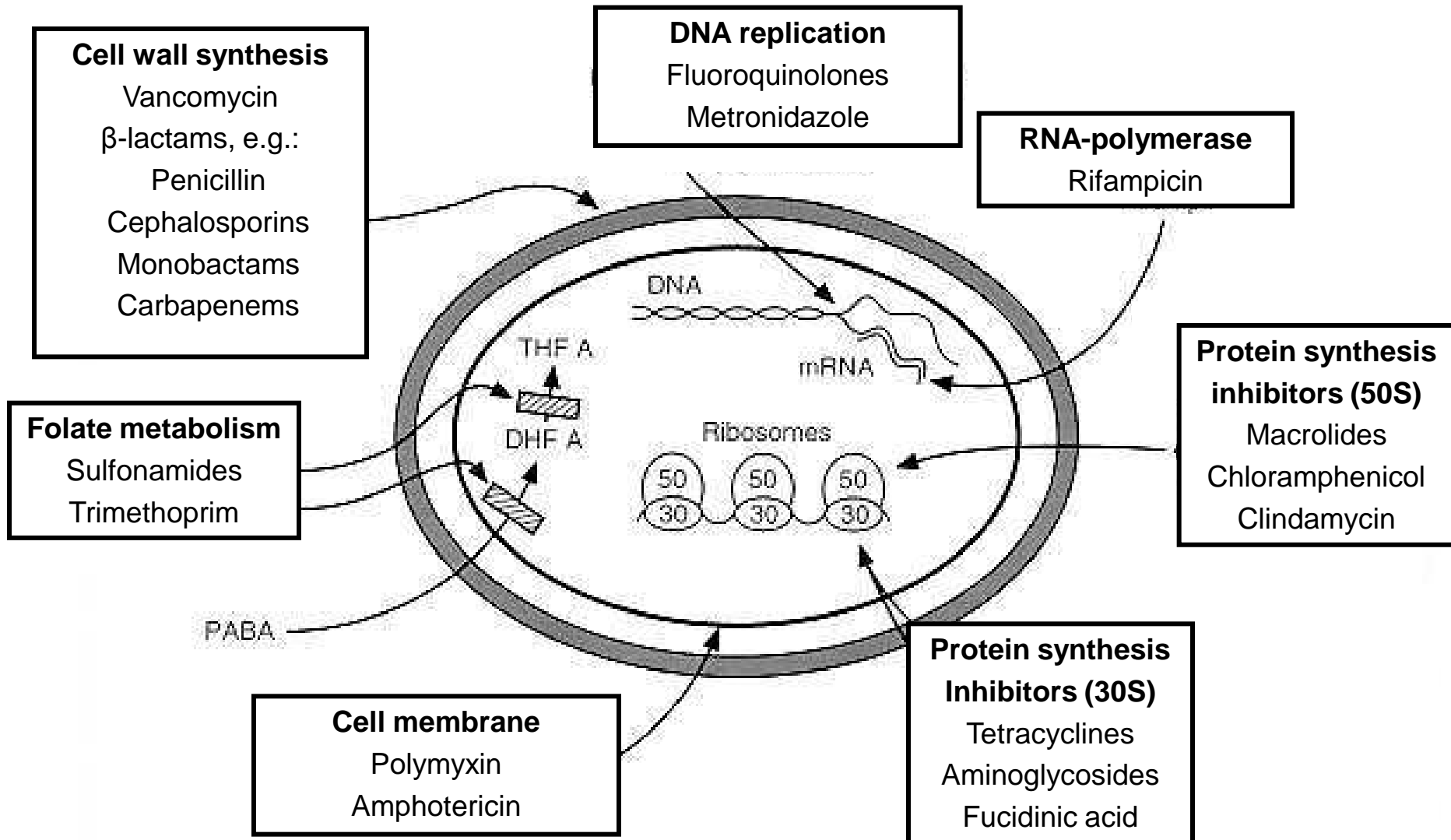
Antimicrobial Resistance Public Meetings

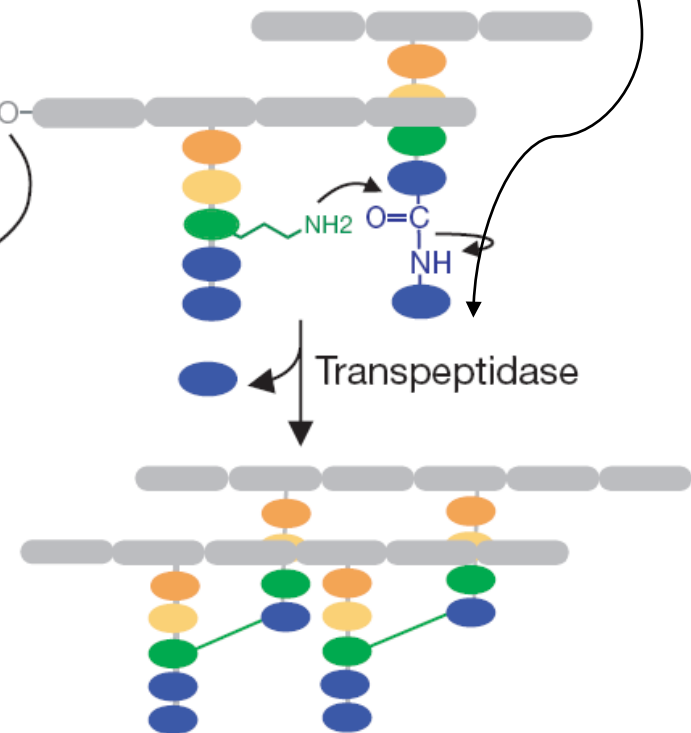
Antimicrobial Resistance

Bacteria and other microorganisms are remarkably resilient and can develop resistance to drugs meant to kill or weaken them. This is known as antimicrobial resistance.



Targets of antimicrobial action





Resistance mechanism

Glycopeptides,
e.g. Vancomycin



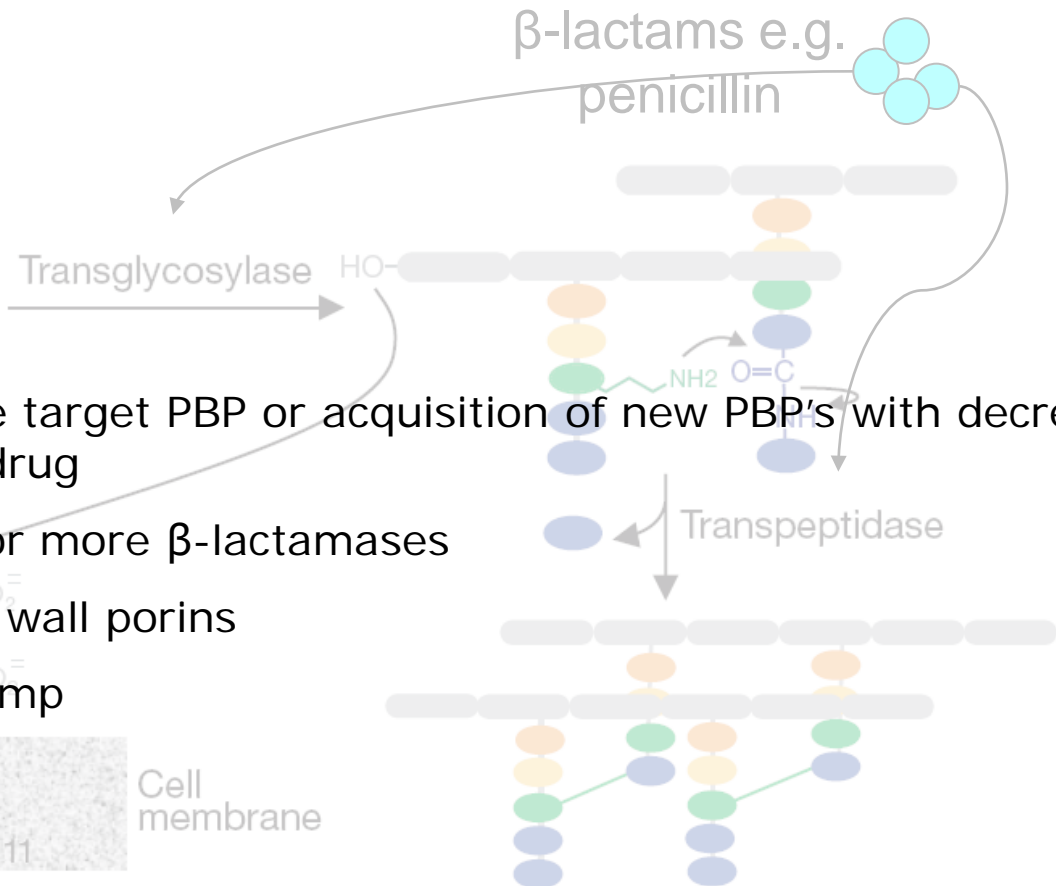
D-Ala
D-Ala
L-Lys
D-Glu
Ala

Against β -lactams:

1. Mutations in the target PBP or acquisition of new PBP's with decreased affinity for the drug
2. Producing one or more β -lactamases
3. Change the cell wall porins
4. Active efflux-pump

Against glycopeptides:

1. Synthesis of D-Ala-D-Lac in stead of D-Ala-D-Ala



Folate pathway inhibitor

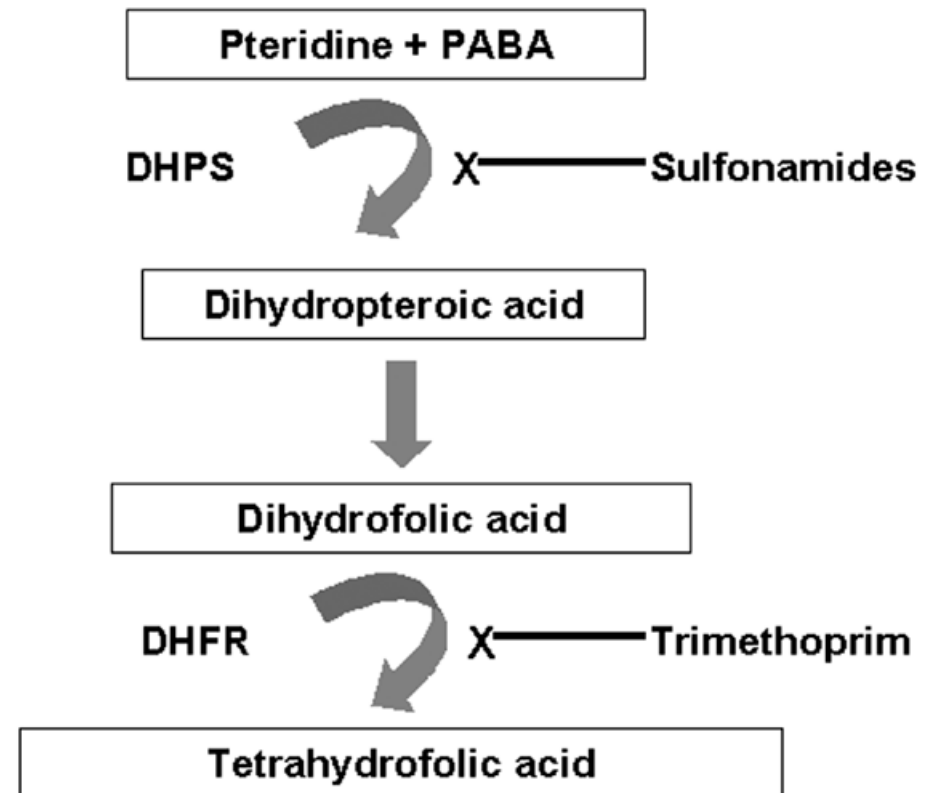


Figure from cdc.gov:

PABA paraaminobenzoic acid

DHPS, dihydropteroate synthase

DHFR, dihydrofolate reductase

Folate pathway

Against sulfonamides:

1. Sulfonamide-insensitive enzymes are produced

Against trimethoprim:

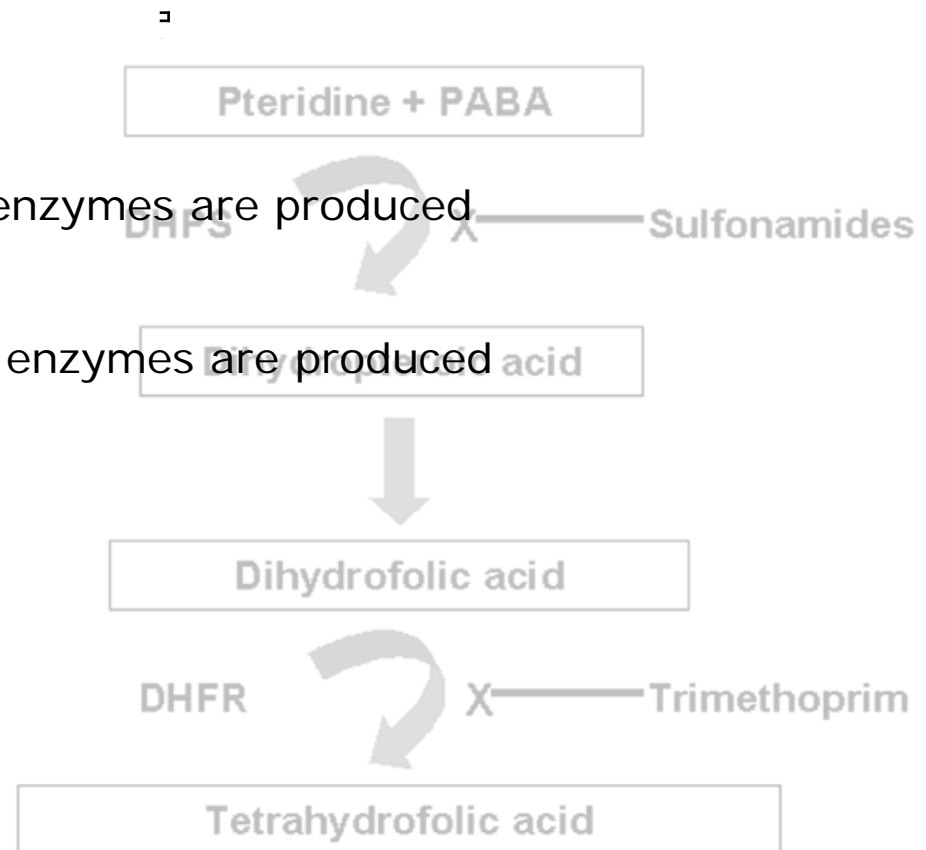
1. Trimethoprim-insensitive enzymes are produced

Figure from cdc.gov:

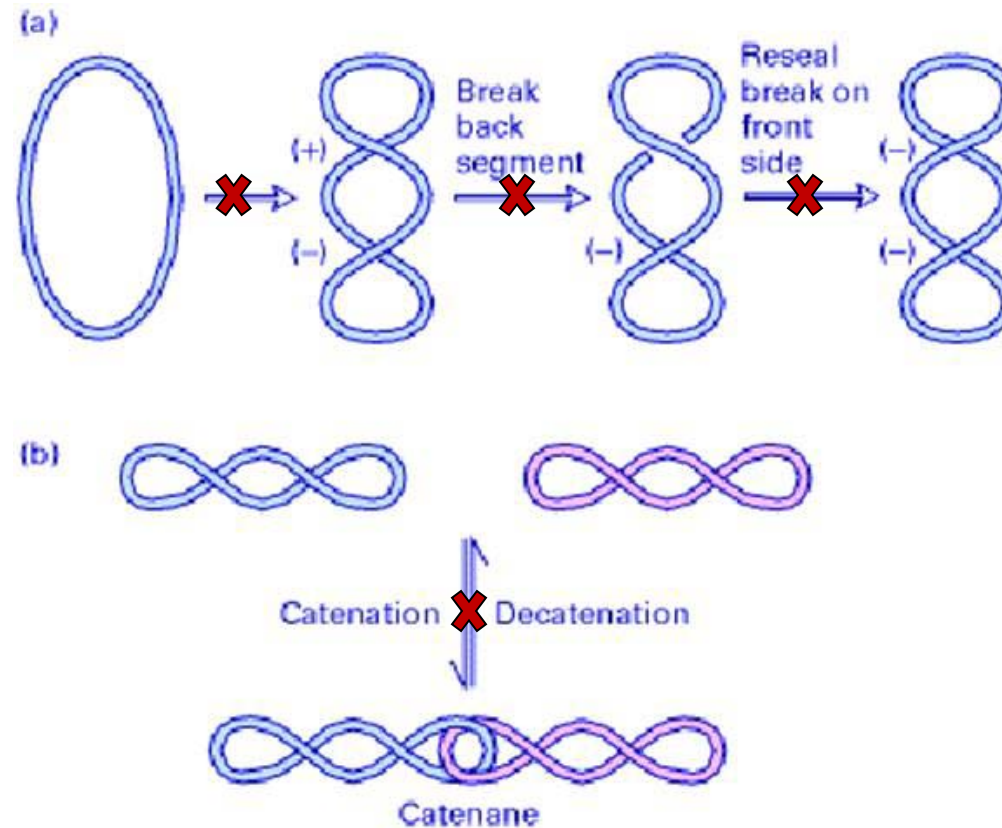
PABA paraaminobenzoic acid

DHPS, dihydropteroate synthase

DHFR, dihydrofolate reductase



Inhibition of DNA synthesis



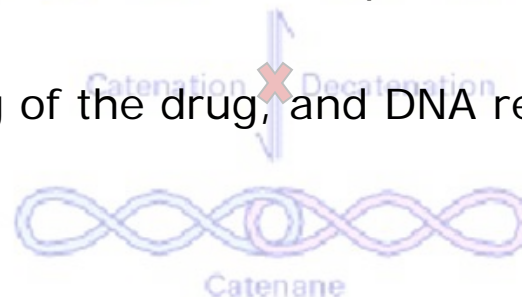
Quinolones appear to mainly target *gyrA* in G⁻ and *parC* in G⁺

Resistance mechanism

1. Target mutations in the topoisomerase genes
2. Decrease permeability of the cell wall
3. Active efflux-pump

(b) High-level fluoroquinolone-resistance: primarily due to mutations in *gyrA* and *parC*-genes

=> reduce binding of the drug, and DNA replication can continue



Quinolones appear to mainly target *gyrA* in G- and *parC* in G+

Inhibition of protein synthesis I

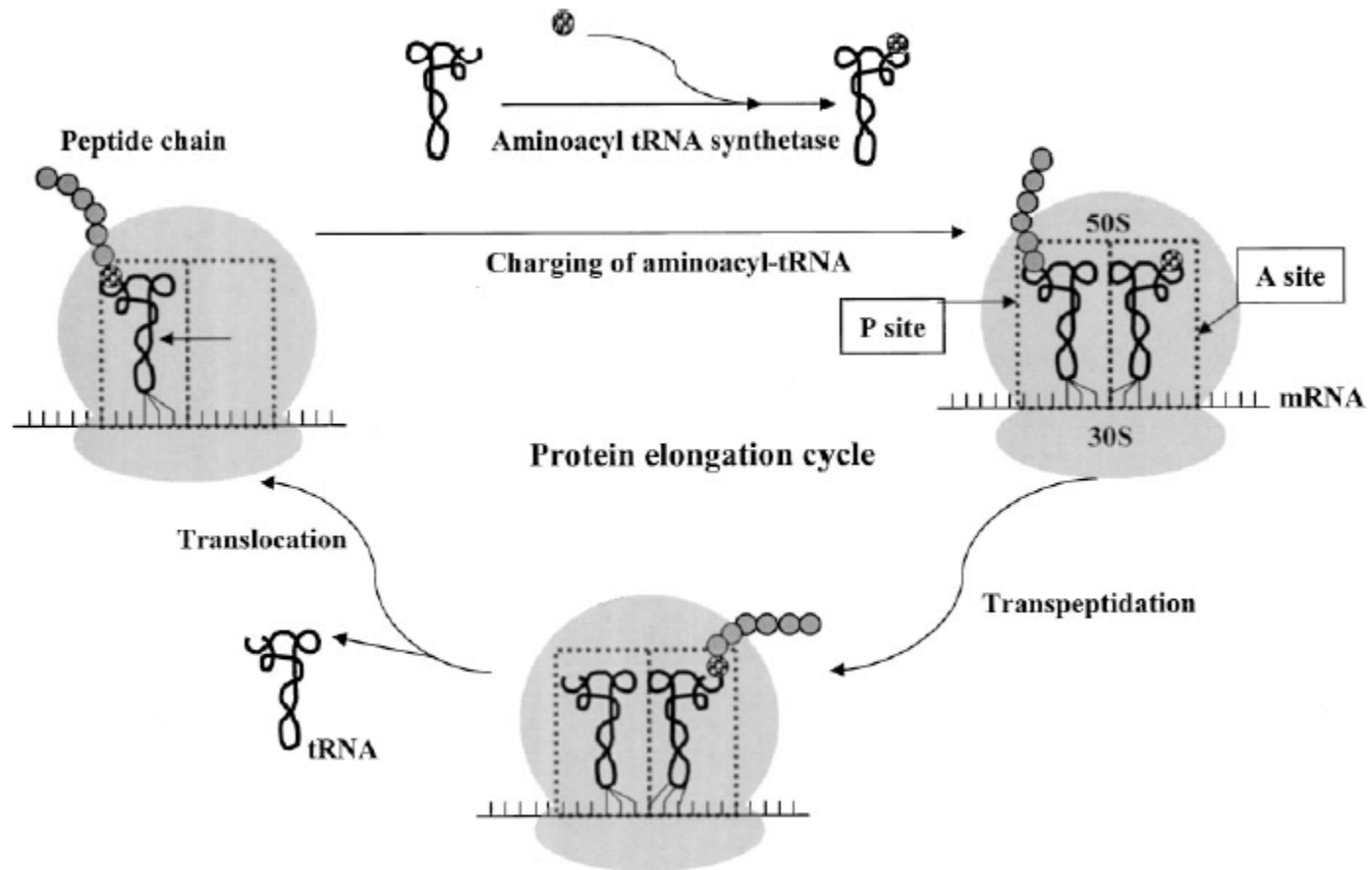


Figure from McDermott *et. al.*, 2003, International Journal of Toxicology, 22:135–143

Inhibition of protein synthesis II

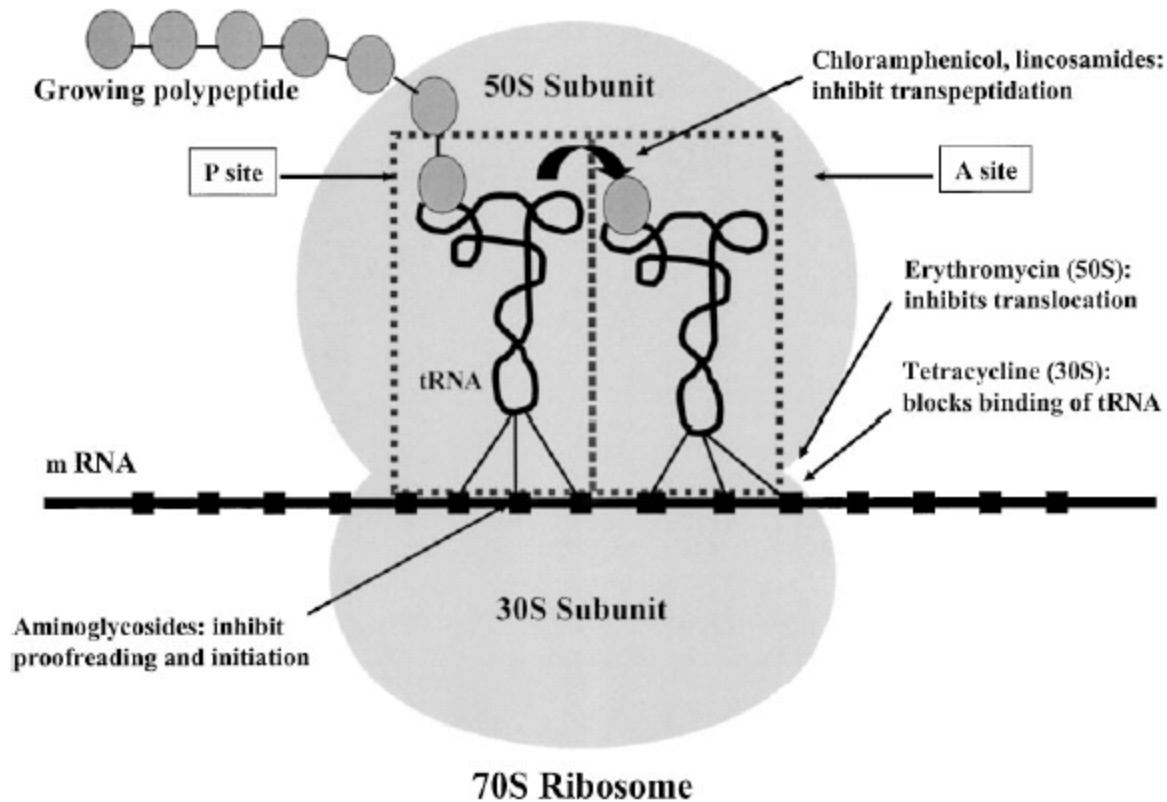


Figure from McDermott *et. al.*, 2003, International Journal of Toxicology, 22:135–143

Resistance mechanism

Against aminoglycosides (e.g. strep, gen):

1. Structural mutations in the 30S ribosomal sub-unit
2. Production of modifying enzymes (a large number of diverse enzymes have been identified)

Against chloramphenicol:

1. Inactivation of the drug by acetylation of the two hydroxyl groups
2. Efflux mechanisms

Against tetracycline:

Against macrolides (e.g. ery):

1. G- are intrinsically resistant
2. Efflux-pump

Against streptogramins:

1. Mutations or modifications (methylation) of the 23S ribosomal RNA subunit
2. Inactivation by acetylation
3. Efflux-pump
4. Ribosomal mutations

Against linezolid:

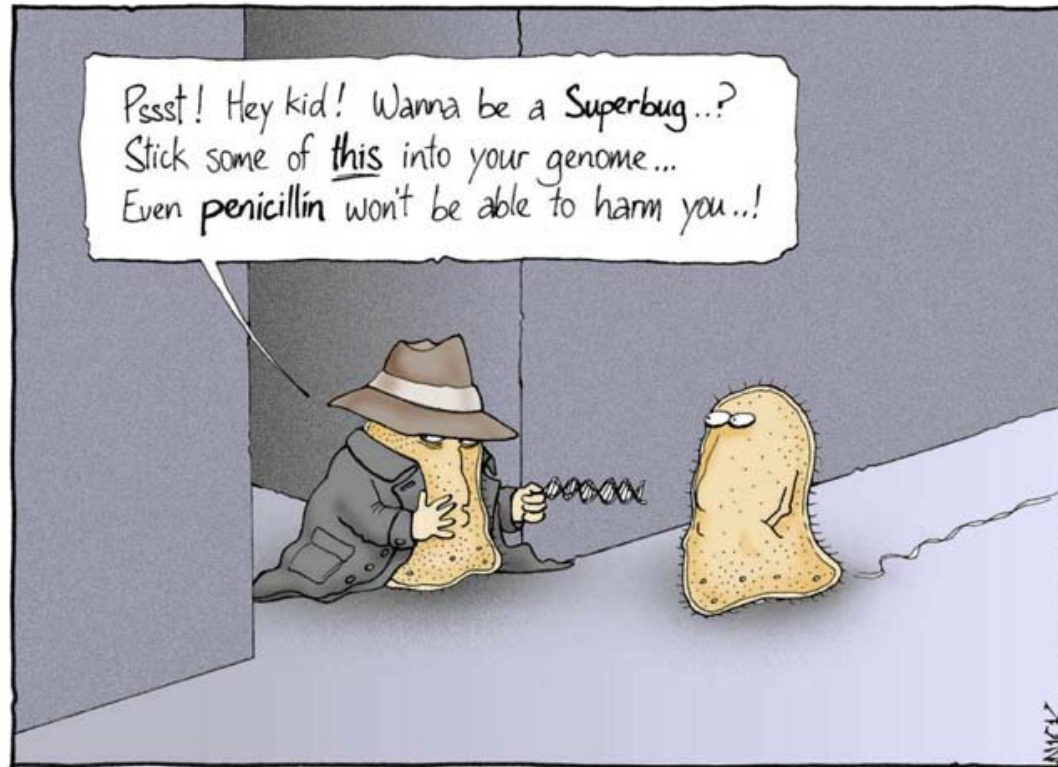
1. Mutations in the 23S rRNA subunit

Mechanisms of resistance

1. Alteration of the antimicrobial agent	Aminoglycosides, chloramphenicol, β -lactams, Streptogramins
2. Mutation in the target site	Aminoglycosides, β -lactams, macrolides, quinolones, rifampicin, trimethoprim, tetracycline, mupirocin
3. Decreased antibiotic accumulation <ul style="list-style-type: none"> - Decreased uptake - Increased efflux 	Many antibiotics Tetracycline, macrolides, chloramphenicol and quinolones
4. Acquisition of drug-insensitive enzyme	Sulfonamides, trimethoprim

Cross resistance

Resistance to two related (avoparcin / vancomycin) or unrelated drugs (erythromycin / lincosamides) is due to a single biological mechanism



Thanks for your attention!